

Title: Systematic comparison of the behaviors produced by computational models of epileptic neocortex

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## Abstract

**Purpose:** We compare two existing models of brain dynamics in epilepsy, one detailed (i.e., realistic) and one abstract (i.e., simplified), in terms of behavioral range and match to *in vitro* mouse recordings. We introduce a method for comparing across computational models that may have very different forms. **Method:** We first extracted high-level metrics from model and *in vitro* output time series. A principal components analysis (PCA) was then performed over these metrics to obtain a reduced set of derived features. These features define a low-dimensional behavior space in which quantitative measures of behavioral range and degree of match to real data can be obtained. **Results:** The detailed and abstract models and the mouse recordings overlapped considerably in behavior space. Both the range of behaviors and similarity to mouse data were similar between the detailed and abstract models. When no high-level metrics were used and PCA was computed over raw time series, the models overlapped minimally with the mouse recordings. **Conclusions:** The method introduced here is suitable for comparing across different kinds of model data and across real brain recordings. It appears that, despite differences in form and computational expense, detailed and abstract models do not necessarily differ in their behaviors.

**Key words:** computational model, model comparison, epilepsy, neocortex, neural networks, time series analysis

## Introduction

The application of computational models to the study of epilepsy is becoming increasingly common. However, many flavors of computational model exist. The choice of model depends on the desired level of detail at which the neural system is modeled, the range of behaviors a model is capable of producing, and the ability of a model to fit to human or animal data. The present study focuses on comparing models differing in level of detail based on their ranges of behavior and fits to real data. We introduce a method to systematically compare any set of models (including models that differ from each other in level of physiological detail) as long as all the model outputs can be expressed as a series of the same kind (e.g. time series of averaged membrane potentials of neurons) that can be further reduced by using a group of quantitative metrics.

For the present discussion, we define a detailed model as one that represents the electrical activity of neurons by biophysical equations that evolve physical variables. These models often explicitly represent both passive membranes and active ion channels within multicompartment neurons that are themselves spatially arranged in a connected network. The physical, electrical, and anatomical properties of these models are derived from and verifiable through comparison to electrophysiological and histological measurements (e.g., Traub and Bibbig, 2000). By contrast, we define an abstract model as one that uses a simplified set of rules that do not model the biophysics directly but instead represent what is considered a minimal set of essential behaviors in a form that is analytically or computationally more tractable. For example, a neuron may be represented as a unit that integrates inputs and spikes when it passes a threshold. Neurons may be embedded in a network topology that trades realism for simplicity. An abstract model may even consist of a set of coupled equations, each representing a population of neurons of the same type. Well-known examples of abstract models can be found in Wilson and Cowan (1973), Fitzhugh (1961), Izhikevich (2003), and Ursano and La Cara (2006). The division between detailed and abstract models is not clear-cut, since all models are simplifications of the

real system; nonetheless, it is useful to make a distinction between models operating at different points on the fidelity-tractability spectrum.

Detailed models have the advantage of having close correspondence between model parameters and biophysical parameters, so that any predictions made by a detailed model are fairly readily translatable into potential manipulations or tests of the real system. On the other hand, having many parameters can make detailed models hard to interpret, as a particular behavior could potentially be produced by many combinations of model parameter values. For understanding how a model's parameters correspond to its behavior, abstract models may prove more tractable. Detailed models, being more biophysically realistic, might also produce a more realistic range of behaviors than would an abstract model. However, this possibility has not, to our knowledge, been formally tested.

In the past, comparisons across different computational models of epilepsy and between computational models and real data have primarily been descriptive and informal. For example, Lytton's (2008) review compares the path to seizure onset in Wendling et al.'s (2002) lumped model to the path to seizure onset in van Dronglen et al.'s (2005) detailed model. Based on visual inspection of plots relating values of excitation and inhibition in the models to model behaviors, Lytton observes that the path to seizure onset is qualitatively different across the two models. Though the observation is highly useful, it is more descriptive than quantitative. Authors of a computational model often visually compare outputs from their model to electrophysiological readings from human or animal models, with a good match taken as evidence in favor of the model. Often, however, it is unclear whether any systematic method was employed for choosing which model outputs and which human/animal traces to compare. For example, the reader may be left to wonder how many human/animal traces the model was unable to match (e.g., Wendling et al., 2002).

Although systematic comparison of computational models to each other and to human/animal data is not currently incorporated into neural modeling methodology, one might expect to find some precedent in computational modeling literature from other fields. Although a search in journal databases

(specifically, the ISI Web of Knowledge and Google Scholar) for terms related to comparison/evaluation of models that attempt to match empirical data yielded few results, the search did turn up a paper by Ortiz et al. (2002) that describes an automated method for comparison of real protein structures and computational models' protein structure predictions. The method addresses the problem that different models can produce output (in their case, protein structures) at different resolutions or at different levels of completeness. Rather than making comparisons based on root mean square distance, their system exploits a more sophisticated method of aligning structures prior to computing distance so that issues of resolution and incompleteness do not unduly affect goodness of fit scores. As with protein structure comparison, there are problems with using root mean square distance for epilepsy model comparison, as discussed in the sections below.

The method introduced in the present study has similar intent to that of Ortiz et al.'s protein structure model comparison, particularly in that it provides systematic quantitative comparison measures and is suitable for use across models that may vary considerably in form and in resolution of the output. However, some aspects of our method, such as description of the size of models' behavior space, expand the scope of comparison beyond that of Ortiz et al. in order to address questions of particular importance in epilepsy modeling. For example, the range of behaviors produced by a model is measured, since (it is desirable that the models be able to produce the diverse range of behaviors exhibited by the mammalian brain, including both non-seizure-like (interictal) and seizure-like (ictal) activity.

## **Method**

In the following paragraphs we describe particulars of the detailed and abstract models used in this study. We also describe comparison data taken from *in vitro* mouse recordings. We then present our analysis pipeline for comparison across models.

### **Detailed model**

The detailed model investigated in this study is a neocortical model described by van Drongelen et al. (2004a) and van Drongelen et al. (2004b). The model includes six neuron types, two of which are

excitatory (superficial and deep pyramidal) and four of which are inhibitory (chandelier, and three types of basket). There are 656 neurons in the neocortical network. Each neuron type is modeled as a set of cell compartments (axon, soma, initial segment, and/or a variable number of dendrite compartments) and contains a combination of voltage-dependent ion channels (sodium, potassium, and optionally persistent sodium, NaP) and the neurons are spatially distributed according to histological measurements from the literature. The neurons connect via synapses (excitatory or inhibitory) and gap-junctions (between inhibitory neurons only). van Drongelen et al. (2004a) and van Drongelen et al. (2004b) have shown that the model can display both normal non-seizure-like and epileptic seizure-like activity depending on the values of the network's excitation and inhibition strength parameters.

For the present study, two versions of the model, one with NaP channels and one without, were explored. We expected that including NaP would produce more realistic activity. For each of these two versions of the model, forty-nine simulations were run, each with a unique combination of excitation and inhibition weights: the synaptic coupling weights found in van Drongelen et al. (2006, Table A1) were scaled by factors ranging from 0 to 3 in steps of 0.5. All possible pairwise combinations of excitation and inhibition values were tested. Each model run produced 5 s of simulated activity. In each run, one of the cells with was injected with  $5 \times 10^{-10}$  A at time 1 s. The output trace used in all comparisons was created by averaging the membrane potential of the cells and downsampling to 1 kHz. Simulations were implemented in pGENESIS (the Parallel GEneral NEural SIMulation System; Bower and Beeman, 1998) and run on the Jazz computing cluster at Argonne National Laboratory. The simulations took about 200 s to run for the with NaP version.

### **Abstract model**

The abstract model investigated in this study was the model from Izhikevich (2003). This model treats each neuron as a single compartment. Different neuron types are created by randomly varying the four parameters of a single neuron template. The neurons have no specified spatial location and are connected all-to-all with random weights, some of which are excitatory and some of which are

inhibitory. Specific voltage-dependent ion channels are not modeled as in the van Drongelen et al. (2004a, 2004b, 2005, 2006) model. Rather, a neuron's membrane potential is determined based on two ordinary differential equations and a spike-resetting rule. As with the detailed model, the abstract model implemented in this study contained 656 neurons. Two versions of the model were run, one of which was identical to Izhikevich's (2003) network except that 656 neurons, rather than 1000, were modeled. In the other version, a uniform 6 ms transmission delay was introduced for all connections with the expectation that including the transmission delay would produce more realistic average membrane potentials. As with the realistic version, there were forty-nine 5 s runs, each with a unique combination of excitation and inhibition scaling factors. Since the Izhikevich (2003) model includes random input to each cell at each timestep, no initial current injection was needed. The membrane potential at each timestep (the simulations occurred at 1 kHz) was averaged across the 656 neurons in the network to create an average membrane potential time series. Simulations were implemented in MATLAB and took about 10 s to run on an ordinary laptop for the no delay version, which is considerably faster than the detailed model execution time.

### **Mouse recordings**

Local field potential recordings of mouse frontal lobe tissue were used to provide a standard to judge the computational models' average activations against. The data consisted of several-minute-long 30 Hz low-pass filtered recordings during which a number of experimental manipulations were performed. The long recordings were broken into ninety-four 5 s chunks, some of which were judged by visual inspection to be seizure-like and others of which were judged to be comparable to normal activity in human tissue.

### **Model comparison pipeline**

Because of the disparate characters of the systems to be compared, a number of potential issues arise when attempting the cross-model comparison. These include choice of the range of model parameters to include, normalization of waveforms, reconciliation of sample rates, choice of signal

duration, sensitivity of root mean square error to particulars of waveform shape, inappropriateness of root mean square error for comparison of analog and binary models, and choice of alternatives to root mean square error. The components of the pipeline described next are designed to address some of these issues within a modular framework that enables swapping of components.

### **Primary metrics**

To focus on characteristics of the signals that were likely to be most relevant to characterizing the features of network activity relevant to epilepsy, we extracted eight primary metrics from the time series. Before calculating these metrics, signals were first low-pass filtered at 30 Hz so that signals from the computational model simulations would be comparable to the low-pass filtered mouse tissue recordings. Also, to exclude any initial transients in the computational model simulations, we used only the portion of each time series from 1.5 s to 5 s.

The first five metrics were taken from the power spectrum of each time series. These included the frequency and the power amplitude of the peak in the power spectrum. They also included the power present in the following classic EEG frequency ( $f$ ) bands:  $\theta$  ( $4 \text{ Hz} < f \leq 8 \text{ Hz}$ ),  $\alpha$  ( $8 \text{ Hz} < f \leq 12 \text{ Hz}$ ), and  $\beta$  ( $12 \text{ Hz} < f \leq 30 \text{ Hz}$ ) (van Drongelen, 2007). The final three metrics were Hjorth's activity, mobility, and complexity (Hjorth, 1970) — classical EEG features. These features are calculated from the standard deviation and the first and second derivatives of the standard deviation of the time series.

Comparisons were also performed with a subset of the metrics, in this case the three Hjorth measures, in order to investigate the sensitivity of the analysis to the choice of metrics. In addition, comparisons were performed based on the raw time series in order to test the extreme case where no derived metrics are used at all.

### **Comparison in principal components space**

The principal components (PCs) and their eigenvalues were computed over eight-element vectors containing the primary metric data (or 3,500-element raw time series vectors, in the case of the supplementary analysis described below). The calculation was performed in R, using the singular value



decomposition based *prcomp* function (R Development Core Team, 2009). We assigned each simulated or measured time series a pair of coordinates calculated by rotating and projecting the time series onto the first and second PC vectors (which we will also refer to as derived features). This procedure maximizes the variance observed across the time series while satisfying the constraint that only two dimensions may be used, enabling meaningful visualization of the simulated or measured network behaviors. In addition, several quantitative measures were calculated in this PC behavior space. We quantified the magnitude of the range of behaviors exhibited by a model (computational or animal) by calculating (1) the area in PC space of the convex hull defined by all the simulations from the model or (2) the average pairwise Euclidean distance in PC space between all the simulations from the model. In addition, we calculated the overlap between two sets of time series (such as that between a model version and the mouse tissue recordings) by taking the average pairwise distance in PC space between the time series in one set and the time series in the other set.

## Results

Figure 1 shows the data from each of the computational and animal models plotted in the behavior space defined by the first two derived feature vector principal components. Note the considerable overlap in this space between points representing simulations from the four computational model versions (two detailed versions and two abstract versions) and from the mouse tissue recordings. Table 1 gives quantitative measurements of the range of each model's behaviors and of the similarity between each computational model's behaviors and that of the mouse recordings.

Figure 2 and Table 2 give visualizations and quantitative measurements that resulted when principal components analysis was performed on the raw time series (i.e., no metrics were calculated). Notice that the variability across the computational models is distributed across the first PC but not across the second, whereas most of the variability in the mouse tissue recordings is distributed across the second PC but not the first. This non-overlap between distributions makes comparison between the computational models and the mouse data difficult. Analysis based on raw time series yielded the result

that all computational model data is judged as being far away from the mouse data. The only exception was the no delay version of the abstract model, which tended to cluster around the origin in principal components space, exhibiting little variance along either principal component.

Based on the figures and quantitative range measures (convex hull size and mean distance between points within a model version) from the PC analysis computed over the eight primary metrics, the computational models and the mouse data all produced roughly the same range of behaviors in PC space. In addition, all the computational models were comparable in their average distance to points in the mouse data and these distances were comparable to distances among data points within the mouse recordings.

## **Discussion**

In this paper, we introduced a method for systematically comparing very different computational models of epilepsy. The method constructs a vector of high-level metrics by applying a prescribed set of analyses on each time series taken from real tissue and/or from models to be compared. Principal components analysis is then used to reduce the collection of primary metrics to a smaller set of derived features. This procedure allows real and simulated data, possibly from very different underlying models, to be visually and quantitatively compared in a low-dimensional behavior space.

We applied this method to compare simulations from a detailed neural model of brain dynamics, simulations from an abstract neural model of brain dynamics, and local field potential recordings from a mouse tissue sample that exhibited both non-seizure-like and seizure-like dynamics. Counterintuitively, it appears that the abstract neural model investigated here may produce as broad a range of behaviors, as measured in the metric-based PC space, as the detailed model we investigated. Thus, at least for the range of excitation and inhibition strengths that we explored, simplification in form does not necessarily lead to a reduced range of behaviors. The abstract model also produced behaviors that were comparable to the detailed model's in their degree of similarity to the mouse data. This result suggests that the advantages and disadvantages of detailed vs. abstract modeling approaches may lie more at the

methodological level, being related to the tradeoff between computational/development efficiency and isomorphism with the structure of the system being modeled, rather than being related to the ability to match behavior of a real system.

A number of future research and development directions are worth pursuing. One is the development of a systematic method for selecting which primary metrics to include. Our conclusions are contingent upon selection of relevant primary metrics, the combination of which the method depends upon to discriminate between various behaviors (for EEG-like signals: quasi-periodic oscillations, sharp waves and spikes, bursts, etc). In this study, we have chosen a subset of popular and well-regarded automated metrics used by epileptologists and epilepsy researchers to characterize EEG activity, and we assumed their appropriateness for comparison of ictal and interictal dynamics. In some cases, the metrics of interest might be known a priori. In other cases, however, many possible metrics may be valuable and an objective and systematic method for selecting among them would be worthwhile.

Additional methods for computing range of behavior within a model and similarity of behaviors might also be worth exploring, since the convex hull and mean pairwise distance measures are sensitive to outliers — a feature that may be undesirable under some circumstances. For example, as Figure 1D shows, the polygon enclosing a set of data points is sometimes far from being uniformly populated. For some purposes, relaxing the constraint that a hull be convex might prove helpful (though relaxation of that constraint complicates the process of determining the hull boundaries).

We hope that in the future similar systematic model comparisons will explore more models and a larger range of parameter values within those models (possibly integrating this comparison approach with parameter search approaches) and that other types of outputs will be compared (such as raster plot characteristics or individual neuron properties) beyond the average activation time series compared here.

Finally, Ortiz et al. (2002) provide an example of formal comparison to human similarity judgments in the field of protein structure modeling. It would be interesting to formally compare the

distances between simulations in the behavior space as calculated here with similarity judgments and ictal vs. interictal classifications made by human EEG experts.

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Table 1. Quantitative measurements based on the data's positions in behavior space based on all 8 derived features.

Model version	Convex hull area	Mean distance within the model version	Mean distance to mouse data
Detailed, no NaP	24	2.7	2.6
Detailed with NaP	20	2.9	2.8
Abstract, no delay	15	2.5	2.5
Abstract with delay	34	2.0	2.2
Mouse tissue	34	2.4	2.3

Table 2. Quantitative measurements based on the data's positions in the space defined by the first two principal components for raw time series (no derived features used).

Model version	Convex hull area	Mean distance within the model version	Mean distance to mouse data
Detailed, no NaP	218	59	51
Detailed with NaP	321	60	52
Abstract, no delay	542	12	21
Abstract with delay	5106	46	45
Mouse tissue	13018	26	26

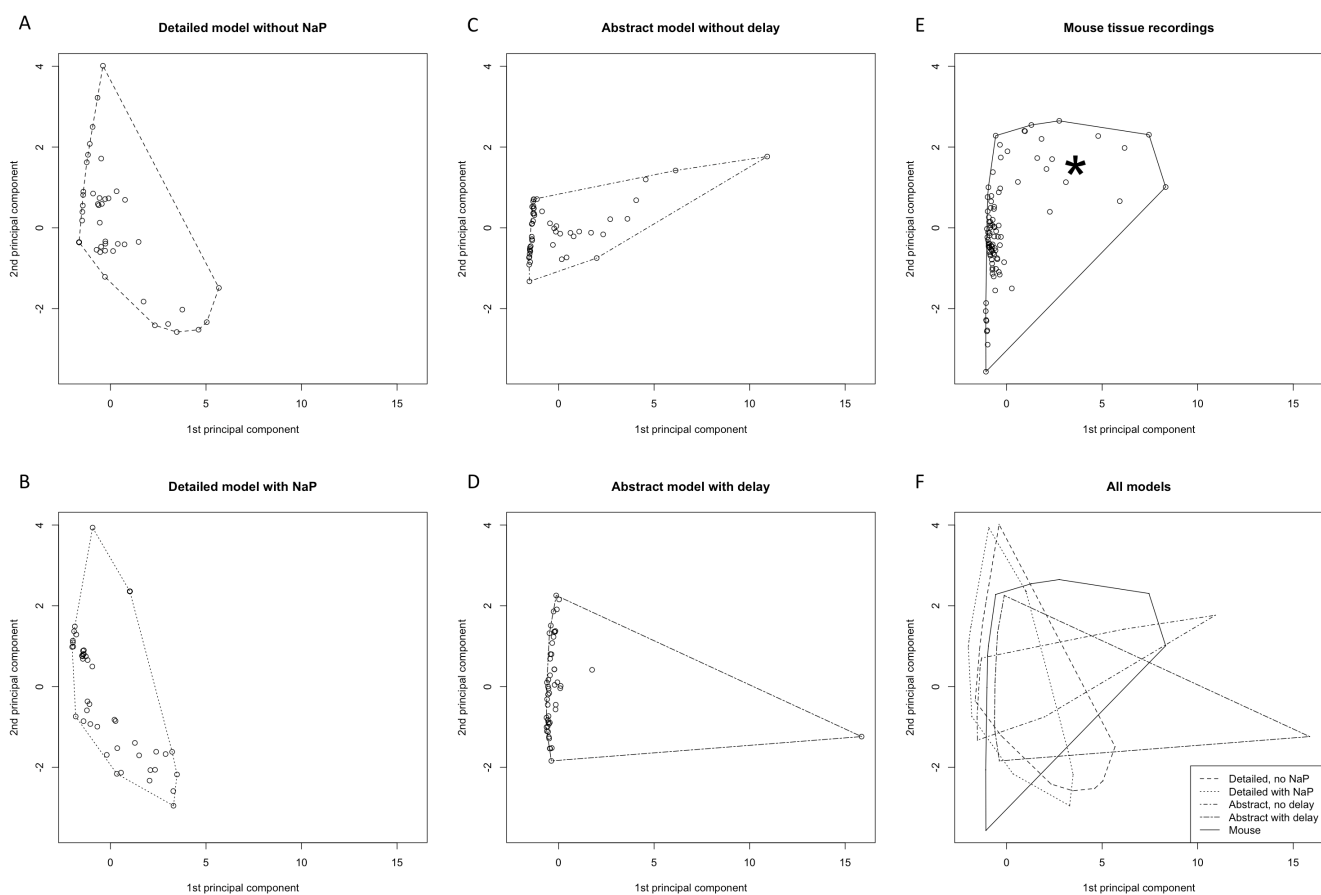


Figure 1. Data plotted in behavior space when PCs are calculated based on the eight metrics derived from simulated or real time series.



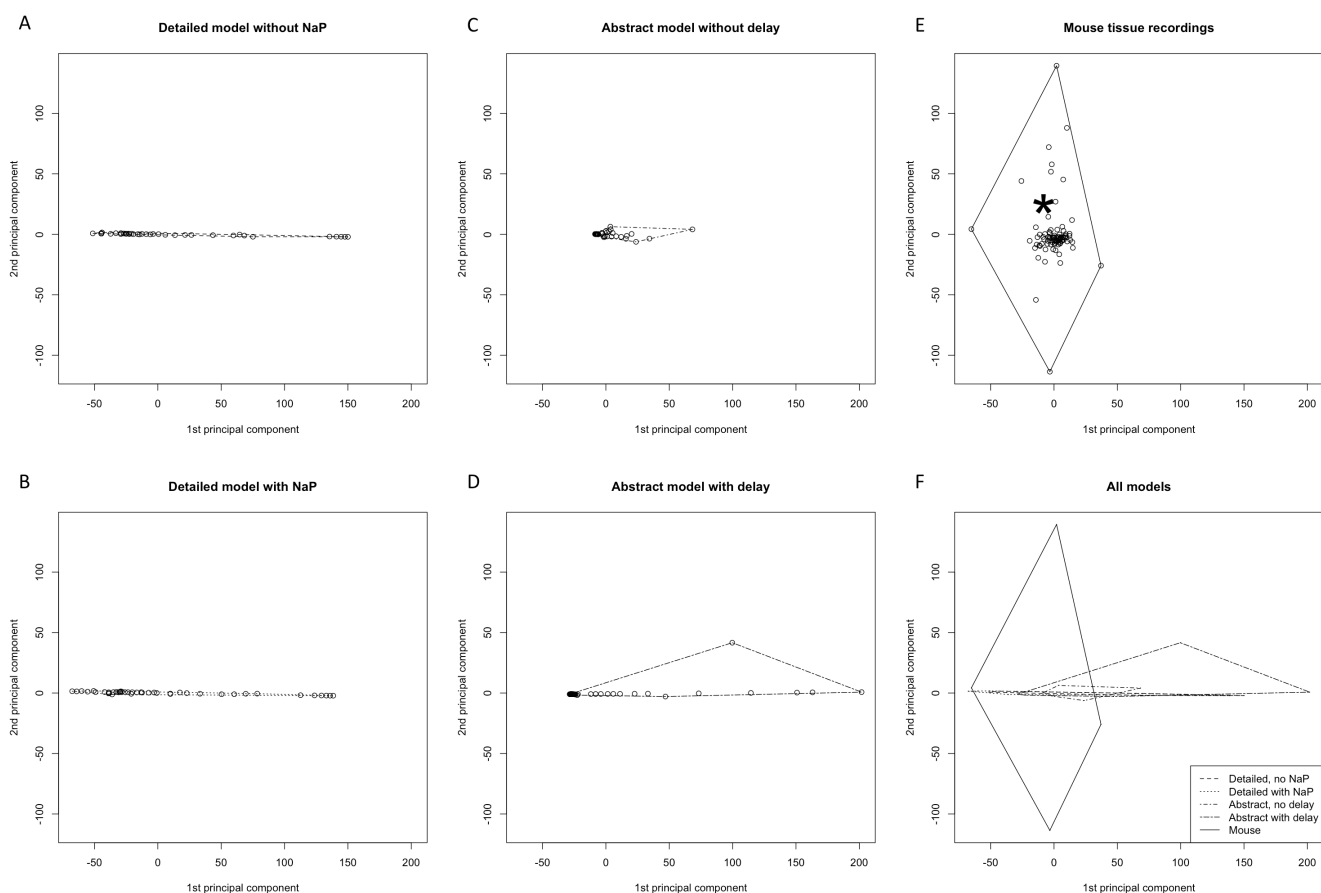


Figure 2. Data plotted against the first two principal components calculated based on raw time series (no metrics calculated).

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